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09/420,433 10/12/99 SIDRANSKY

D JHU1180-1

HM12/0622  
SPENSLEY HORN JUBAB & LUBITZ  
1880 CENTURY PARK EAST  
FIFTH FLOOR  
LOS ANGELES CA 90067

EXAMINER

JOHANNSEN, D

ART UNIT

PAPER NUMBER

1655

DATE MAILED:

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

## Office Action Summary

Application No.

09/420,433

Applicant(s)

Sidransky

Examiner

Diana Johannsen

Group Art Unit

1655



☒ Responsive to communication(s) filed on Oct 12, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

### Disposition of Claims

☒ Claim(s) 1-18 is/are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 1-18 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

### Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

### Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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## DETAILED ACTION

### *Priority*

1. It is noted that this application is a continuation of Application No. 08/181,664, filed January 14, 1994, now U.S. Patent No. 6,025,127. The first line of the specification should be amended so as to provide the current status of the '664 application (i.e., to insert the phrase "now U.S. Patent No. 6,025,127").

### *Claim Rejections - 35 U.S.C. § 112*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite due to the improper expression of alternative limitations in claim

1. Claim 1 recites the phrase "selected from the group consisting of a tumor margin, a regional lymph node, the method comprising....". "Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group,

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recites members as being 'selected from the group consisting of A, B and C'." (MPEP 2173.05(h)). To overcome this rejection, claim 1 may be amended to recite "selected from the group consisting of a tumor margin and a regional lymph node, the method comprising..." "and" in line 10 where it now recites "or".

Claims 2-3 and 11 are indefinite over the recitation of the phrases "amplified before detecting" in claim 2 and "cloned before detecting" in claim 11. It is unclear as to whether the term "detecting" in these phrases is intended to refer back to the "detecting" of claim 1, or whether these phrases are intended to set forth additional, separate method steps. As it is unclear as to how the claims are intended to further limit claim 1, the metes and bounds of the claims are unclear.

Claim 4 is indefinite over the recitation of the phrase "a corresponding wild-type nucleic acid". It is unclear as to what is meant by the term "corresponding". Specifically, it is unclear as to what type of relationship between a target nucleic acid and a wild-type nucleic acid would be required by this language. Clarification is required.

Claim 6 is indefinite because it is unclear as to whether and how it further limits claim 5, from which it depends. Claim 6 sets forth a Markush group from which "the tumor suppressor gene" is to be selected. However, claim 5 does not require a tumor suppressor gene, but rather "an oncogene or a tumor suppressor gene". Thus, it is unclear as to how claim 6 may further limit claim 5 as claim 5 may be limited to oncogenes.

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Claims 12-17 are indefinite over the recitation of the term "preferentially hybridizes". A clear and precise definition for this term is not provided in the specification, and this term does not have a well established meaning in the art. Accordingly, it is unclear as to what types of hybridization would be encompassed by the language "preferentially hybridizes". For example, would such language require specific hybridization to a target, hybridization under stringent conditions to a target, etc.? Clarification is required.

Claims 12-18 are indefinite over the recitation of the term "neoplastic nucleic acid". The specification states that this term "refers to a nucleic acid sequence which directly or indirectly is associated with or causes a neoplasm". While the phrase "causes a neoplasm" is clear, it is not clear as to what types of nucleic acids would be encompassed by the language "directly or indirectly associated with...a neoplasm". Particularly, it is unclear as to what would be encompassed by the term "associated" (i.e., does this refer to a physical association, a type of "association" with disease, etc.), and as to what types of associations would be considered "direct" and/or "indirect". Accordingly, the types of nucleic acids encompassed by the term "neoplastic nucleic acid" are unclear.

Claim 17 is indefinite over the recitation of the limitation "said neoplastic acid". There is insufficient antecedent basis for this limitation in the claims.

Claim 18 is indefinite over the recitation of the limitation "the nucleic acid present in the specimen". It is unclear as to whether this language intended to refer back to the "mammalian

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target neoplastic nucleic acid", or to some other nucleic acid (e.g., genomic nucleic acid from the specimen). Clarification is required.

***Claim Rejections - 35 U.S.C. § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1-3, 5, 10, 12-14, and 17-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]).

Sobol et al teach methods for detecting carcinoma metastases comprising extraction of nucleic acids from a sample of tissue or fluid and detection of a "carcinoma associated sequence" (see entire reference). The samples analyzed by Sobol et al's methods may include both fluids and tissues, including lymph nodes (see, e.g., col 4, lines 52-59). Sobol et al teach that conventional diagnostic methods may fail to detect residual or metastatic disease, and disclose that their methods are more sensitive than conventional methods, including histological analysis (see, e.g., col 2, lines 13-52; col 4, lines 33-35; col 5, lines 28-35). With respect to claims 2-3, Sobol et al's methods comprise amplification with oligonucleotides that flank a target sequence (see entire reference, especially col 4, lines 4-8). With respect, to claims 5 and 17, Sobol et al's methods

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encompass detection of both oncogenes and other "carcinoma associated sequences" (see, e.g., col 4, lines 27-29). With respect to claim 13, Sobol et al disclose that PCR is sufficiently sensitive to detect a target nucleic acid present in only 1 of 10,000 cells (col 2, lines 46-52). With respect to claim 14, Sobol et al disclose that their methods are sufficiently sensitive to detect targets in histologically normal tissue (see, e.g., col 2, lines 13-52; col 4, lines 33-35; col 5, lines 28-35). With respect to claim 18, it is an inherent property of the sample types disclosed by Sobol et al that they are "external to a primary neoplasm".

***Claim Rejections - 35 U.S.C. § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 4, 6, and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]) in view of Effert et al (J. Urology 147:789-793 [2/1992]).

Sobol et al teach methods for detecting carcinoma metastases comprising extraction of nucleic acids from a sample of tissue or fluid and detection of a "carcinoma associated sequence" (see entire reference). The samples analyzed by Sobol et al's methods may include both fluids and tissues, including lymph nodes (see, e.g., col 4, lines 52-59). Sobol et al teach that conventional

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diagnostic methods may fail to detect residual or metastatic disease, and disclose that their methods are more sensitive than convention methods, including histological analysis (see, e.g., col 2, lines 13-52; col 4, lines 33-35; col 5, lines 28-35). Sobol et al teach a variety of targets that may be analyzed by their methods, but do not specifically teach or suggest employing their methods to detect a "mutated tumor suppressor" or targets containing "a mutation, a restriction fragment length polymorphism, a nucleic acid deletion, or a nucleic acid substitution", as required by claims 4 and 15. Further, with respect to claims 6 and 16, Sobol et al do not teach or suggest detection of p53 or the other tumor suppressors recited in claim 6. Effert et al disclose that p53 mutations, which are "most commonly single point mutations", may be detected both in primary tumor samples and in samples from sites of metastasis, including lymph nodes (see entire reference). In view of the teachings of Effert et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Sobol et al so as to have practiced methods of detecting p53 mutations on histologically normal lymph node tissues from prostate carcinoma patients. Effert et al disclose that mutations present at metastatic sites, particularly lymph nodes, may play a role in "the progression of human prostate cancer" (p. 789), and Sobol et al disclose that their amplification based detection methods may be employed to detect metastasis in tissues that appear normal by histological analyses. Accordingly, an ordinary artisan would have been motivated to have modified the method of Sobol et al for the advantage of achieving early, rapid and sensitive detection of carcinoma metastasis.

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8. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al in view of McAnalley et al (U.S. Patent No. 5,587,364 [12/24/1996; effective filing date 7/27/1990]).

The teachings of Sobol et al are set forth in paragraph 7, above. Sobol et al do not teach or suggest detecting "cancer associated sequences" that are associated with benign neoplasms or with head and neck tumors, as required by instant claims 7-9. McAnalley et al disclose a variety of tumor types that cause disease in animals, including benign neoplasms and malignant tumors of the head and neck (col 16, line 43-col 17, line 5). In view of the teachings of McAnalley et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Sobol et al so as to have detected nucleic acid targets associated with benign neoplasms and/or head and neck tumors, as well as other tumor types, in samples from regional lymph nodes and/or tumor margins. An ordinary artisan would have been motivated to have made such a modification for the advantage of achieving early, rapid, and sensitive detection of tumor transformation and/or metastasis.

9. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sobol et al in view of Mullis et al (U.S. Patent No. 4,683,195 [7/28/1987]).

The teachings of Sobol et al are set forth in paragraph 7, above. Sobol et al do not teach or suggest a step of cloning amplified target sequences prior to detection. Mullis et al disclose that the cloning of amplification products allows one to rapidly sequence or express a target molecule of interest (see, e.g., col 15, line 16-col 16, line 13). In view of the teachings of Mullis et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the

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invention was made to have modified the method of Sobol et al so as to have cloned amplification products comprising "carcinoma associated sequences". An ordinary artisan would have been motivated to have made such a modification in order to have, for example, sequenced such products for the advantage of confirming the sequence of a target nucleic acid detected at a metastatic site, or for the advantage of rapidly detecting the presence of novel mutations in such a sequence.

### ***Double Patenting***

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,025,127. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

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The instant claims are drawn to methods for detecting metastases, "neoplastic" nucleic acids, and nucleic acids that contribute "to the etiology of a neoplasm". Instant claims 1-11 and 18 require steps of extracting nucleic acid from a tumor margin or lymph node (claims 1-11) or a tissue specimen "external to a primary neoplasm" (claim 18), and detecting target nucleic acid. Instant claims 12-17 require steps of isolating tissue from a surgical margin or lymph node and detecting hybridization of a probe to said tissue. The instant claims encompass methods in which nucleic acids are amplified and detected (see instant claims 2-3). The '127 claims are drawn to methods for detecting mutated target nucleic acids and methods "for detecting the presence of a mammalian target nucleic acid which contributes to the etiology of a neoplasm". The '127 claims require steps of amplifying target nucleic acids with oligonucleotides that hybridize thereto. The '127 claims set forth target tissue types that include tumor margins and lymph nodes. The instant claims differ from the '127 claim in that the broadest of the instant claims do not require amplification, and in that the instant claims do not require the use of particular oligonucleotides in detection. However, the instant claims are sufficiently broad so as to encompass the '127 claims, and it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the '127 claims so as to have eliminated some of the limitations of the '127 claims (e.g., the requirement for particular oligonucleotides) so as to have arrived at the instant claims. An ordinary artisan would have been motivated to make such a modification for the advantage of, e.g., increasing the number of different tumor types that could

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be detected by the claimed method. Accordingly, the instant claims and the '127 claims are not patentably distinct from each other.

*Conclusion*

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday from 7:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at 703/308-1152. The fax phone number for the Technology Center where this application or proceeding is assigned is 703/305-3014 or 305-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana Johannsen

June 16, 2000

  
W. Gary Jones  
Supervisory Patent Examiner  
Technology Center 1600

6/16/00